Abstract

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Project Title: Allosteric Modulators of D1 Receptors

Abstract: *DESCRIPTION* (provided by applicant): The proposal will use high throughput screening (HTS) of chemical libraries to identify allosteric modulators of D1 dopamine receptors. Allosteric modulators hold great promise as therapeutics because they provide activity-dependent spatial, temporal, and receptor specificity. Specific Aim 1 shall provide initial validation tests and reagents to the appropriate MLSC to establish a cell-based assay as a tool to identify compounds acting as positive allosteric modulators of D1 dopamine (D1) receptors. In the proposed cell model, D1-stimulated increases in cyclic AMP lead to activation of the cyclic AMP response element (CRE) which then leads to increase luciferase expression (Luc) that can be measured in a high throughput setting. We have previously used this model to screen successfully a small (2000 compounds) chemical library supplied by NCI. We propose to validate and establish the assay performance minimums required for HTS using equipment within one of the MLSCN's HTS Centers. Specific Aim 2 will use the validated D1-CRE-Luc cell model to perform a large scale HTS screen to identify allosteric modulators of D1 dopamine receptors. Compounds identified here will be subjected to a follow up HTS in the presence of a non-selective activator of adenylate cyclase, forskolin. This high throughput follow-up screen will be used to minimize rapidly false positives that have actions inconsistent with those of a D1 dopamine receptor allosteric modulator. Specific Aim 3 will validate potential lead compounds as allosteric modulators of D1 dopamine receptors using a HTS cyclic AMP accumulation assay as a more direct readout of D1 receptor function. These experiments will include concentration-response curves in the absence and presence of dopamine to examine the potency and the activity of each allosteric modulator. Specific Aim 4 seeks to identify potential structural classes of compounds by mining chemical libraries and performing chemical synthesis. Each series of structurally-related compounds will then be subjected to the pharmacological studies described in Specific Aim 3 to identify the structure-activity relationships. All compounds from these screens will be directly deposited into PubChem to promote information sharing. Relevance to Public Health: Dopamine receptors are critical neuroreceptors that are involved motor function, memory, mood, and drug addiction. The D1 dopamine receptor has been identified as a key target associated with Parkinson's disease and schizophrenia. We propose to identify new chemical probes that can be used to safely and effectively modulate D1 dopamine receptors to improve human health.

Thesaurus Terms:
High throughput screening, dopamine receptor, D1, MLSC, MLSCN, luciferase, Luc, AMP, CRE, allosteric modulator, adenylate cyclase, forskolin, Parkinson's disease, schizophrenia, chemical probes

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